

3-Benzyl-2-(4-fluorophenyl)-1,3-thiazolidin-4-one

Alexander Gutiérrez,^a Braulio Insuasty,^b Justo Cobo^c and Christopher Glidewell^{d*}^aCiudadela Universitaria, Universidad Tecnológica del Chocó, AA 292 Quibdo, Colombia, ^bDepartamento de Química, Universidad de Valle, AA 25360 Cali, Colombia, ^cDepartamento de Química Inorgánica y Orgánica, Universidad de Jaén, 23071 Jaén, Spain, and ^dSchool of Chemistry, University of St Andrews, Fife KY16 9ST, Scotland

Correspondence e-mail: cg@st-andrews.ac.uk

Received 23 September 2010

Accepted 31 October 2010

Online 8 December 2010

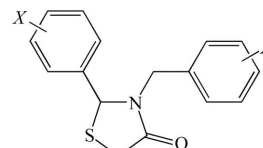
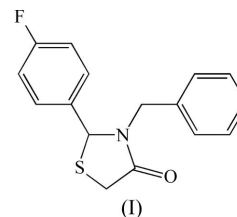
The title compound, C₁₆H₁₄FNOS, crystallizes with $Z' = 2$ in the space group $P2_1/c$. In one of the two independent molecules, the heterocyclic ring is effectively planar, but in the other molecule this ring adopts an envelope conformation. The molecules are weakly linked by two C—H...O hydrogen bonds to form $C_2^2(14)$ chains. Comparisons are made with some symmetrically substituted 2-aryl-3-benzyl-1,3-thiazolidin-4-ones.

Comment

In our synthetic search for new bioactive compounds, we have recently focused on the preparation of thiazol-4-one derivatives, which have shown a wide range of pharmacological activities (Insuasty *et al.*, 2010, and references therein), *i.e.* antibacterial, antifungal, antimicrobial, antiviral and anti-convulsant activity. We report here the structure of the title compound, (I) (Fig. 1), an asymmetrically substituted 2-aryl-3-benzyl-1,3-thiazolidin-4-one derivative, which we compare with the series of symmetrically substituted analogues (Cunico *et al.*, 2007), compounds (II)–(VI) (see Scheme). Compound (I) was prepared in excellent yield using a three-component cyclocondensation reaction between benzylamine, 4-fluorobenzaldehyde and mercaptoacetic acid. By contrast, compounds (II)–(VI) were all prepared using the reactions of aryl aldehydes with L-valine [(*S*)-2-amino-3-methylpropionic acid] and mercaptoacetic acid (Cunico *et al.*, 2006). In all of (I)–(VI), atom C2 in the heterocyclic ring is a stereogenic centre, but all of the compounds are formed as racemic mixtures, despite the presence of an enantiomerically pure amino acid in the synthesis of (II)–(VI).

Compound (I) crystallizes with $Z' = 2$ in the space group $P2_1/c$, and in the selected asymmetric unit, molecule 1, containing atom S11 (Fig. 1), has the *R* configuration at atom C12, while molecule 2, containing atom S21, has the *S*

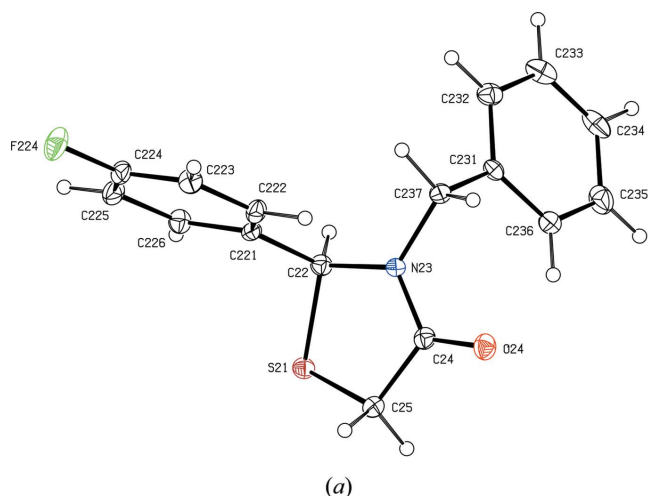
configuration at atom C22. Compounds (II)–(VI) all crystallize with $Z' = 1$, either in the space group $C2/c$ [(V)], or in space groups $P2_1/c$ or $P2_1/n$ [(II)–(IV) and (VI)], but the cell dimensions of (I) bear no close resemblance to those in any of (II)–(VI).



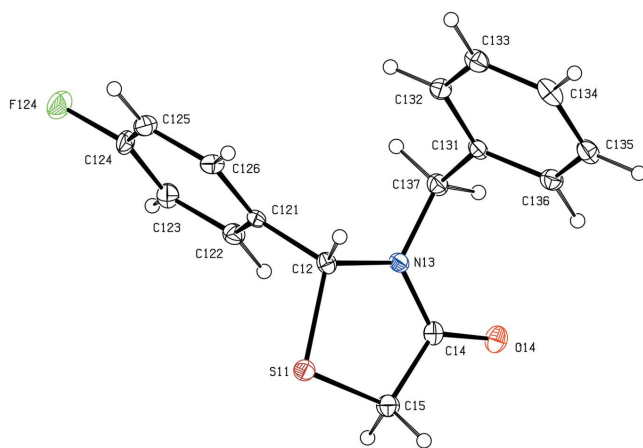
In molecule 1 of (I), the heterocyclic ring is effectively planar, with a maximum deviation from the mean plane through the ring atoms of only 0.021 (3) Å for atom C15. However, the corresponding ring in molecule 2 adopts an envelope conformation, folded across the line C22...C25, with ring-puckering parameters (Cremer & Pople, 1975) for the atom sequence S21—C22—N23—C24—C25 of $Q_2 = 0.220$ (3) Å and $\varphi_2 = 184.4$ (8)°. Similar envelope conformations were observed in each of (III)–(VI), but in (II) the heterocyclic ring adopts a half-chair conformation, twisted about the S1—C5 bond (Cunico *et al.*, 2007). It seems likely that the saturated heterocyclic rings in (I)–(VI) are all fairly flexible and that their detailed conformations may, to some extent, be a reflection of direction-specific intermolecular forces.

The molecules of (I) are weakly linked into chains by two C—H...O hydrogen bonds (Table 1), but C—H... π (arene) hydrogen bonds and aromatic π – π stacking interactions are absent, despite the presence of four independent and relatively unencumbered aryl rings in the asymmetric unit. Within the selected asymmetric unit, the two molecules are linked by a hydrogen bond having atom O14 as the acceptor, and dimeric units of this type, related to one another by translation, are linked by a second hydrogen bond having atom O24 as the acceptor, so giving rise to a $C_2^2(14)$ (Bernstein *et al.*, 1995) chain running parallel to the [100] direction (Fig. 2).

There is a reasonably short C—H...F contact in (I) involving atom F124, but no corresponding contact occurs involving atom F224. However, this contact should not be regarded neither as a hydrogen bond nor indeed as structurally significant, as it has been established that halogen atoms bonded to C atoms are extremely poor acceptors, even from O—H or



(a)



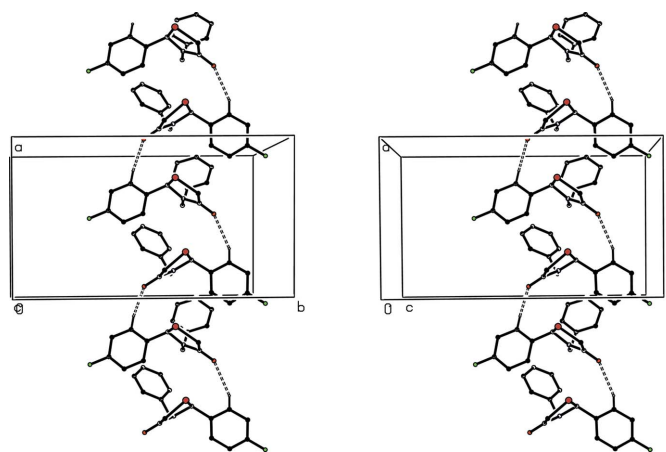
(b)

Figure 1

The independent molecules of (I), showing the atom-labelling schemes. (a) A type 1 molecule having the *R* configuration at atom C12, and (b) a type 2 molecule having the *S* configuration at atom C22. Displacement ellipsoids are drawn at the 30% probability level.

N—H, and worse from C—H (Howard *et al.*, 1996; Aakeröy *et al.*, 1999; Brammer *et al.*, 2001; Thallapally & Nangia, 2001).

It is of interest briefly to compare the structure of asymmetrically substituted (I) with those of symmetrically disubstituted (II)–(VI) (Cunico *et al.*, 2007), all of which, as noted earlier, crystallize with $Z' = 1$. In the difluoro compound, (II), where the 2-aryl ring, but not the benzyl ring, exhibits orientational disorder over two sets of sites, a combination of C—H···O and C—H··· π (arene) hydrogen bonds links the molecules into sheets, which are themselves linked in pairs by an aromatic π – π stacking interaction. Thus, the direction-specific intermolecular forces which are manifest in the structure of the difluoro compound, (II), differ significantly from those in the monofluoro compound, (I). The two isomeric dimethoxy compounds, (III) and (IV), present very different patterns of behaviour. There are no direction-specific intermolecular interactions of any type in the crystal structure of (III), but in (IV), a combination of C—H···O and C—H··· π (arene) hydrogen bonds links the molecules into sheets. In a somewhat

**Figure 2**

A stereoview of part of the crystal structure of (I), showing the formation of a hydrogen-bonded $C_2^2(14)$ chain parallel to [100]. For the sake of clarity, H atoms not involved in the motif shown have been omitted.

similar way, the isomeric dinitro compounds, (V) and (VI), again show different modes of molecular aggregation. In (V), a C—H··· π (arene) hydrogen bond combines with three independent C—H···O hydrogen bonds to link the molecules into sheets, while in (VI), the molecules are linked into chains of fused rings by the action of four independent C—H···O hydrogen bonds. Thus, the supramolecular aggregation is significantly different in each member of this series of rather similar compounds, (I)–(VI).

Experimental

A solution of equimolar amounts (9.4 mmol of each component) of benzylamine, 4-fluorobenzaldehyde and mercaptoacetic acid in anhydrous benzene (10 ml) was heated under reflux for 8 h. The reaction mixture was then allowed to cool to ambient temperature, after which it was washed with aqueous sodium hydrogen carbonate solution (10 ml of a 2% solution). The organic phase was dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The solid residue was purified by crystallization from ethanol to give colourless crystals of (I) which were suitable for single-crystal X-ray diffraction (yield 96%, m.p. 367–368 K). MS (EI, 70 eV) m/z (% abundance): 287 (4, M^+), 212 (23), 196 (32), 147 (52), 104 (38), 91 (100), 28 (28).

Crystal data

$C_{16}H_{14}FNOS$
 $M_r = 287.34$
 Monoclinic, $P2_1/c$
 $a = 9.6931$ (9) Å
 $b = 16.8888$ (16) Å
 $c = 16.4202$ (18) Å
 $\beta = 94.706$ (12)°

$V = 2679.0$ (5) Å³
 $Z = 8$
 Mo $K\alpha$ radiation
 $\mu = 0.25$ mm⁻¹
 $T = 120$ K
 $0.45 \times 0.40 \times 0.14$ mm

Data collection

Bruker–Nonius KappaCCD area-detector diffractometer
 Absorption correction: multi-scan (SADABS; Sheldrick, 2003)
 $T_{\min} = 0.868$, $T_{\max} = 0.966$

58245 measured reflections
 4986 independent reflections
 2857 reflections with $I > 2\sigma(I)$
 $R_{\text{int}} = 0.124$

Table 1
Hydrogen-bond geometry (Å, °).

<i>D</i> —H··· <i>A</i>	<i>D</i> —H	H··· <i>A</i>	<i>D</i> ··· <i>A</i>	<i>D</i> —H··· <i>A</i>
C126—H126···O24 ⁱ	0.95	2.56	3.193 (4)	125
C226—H226···O14	0.95	2.49	3.354 (4)	151

Symmetry code: (i) *x* + 1, *y*, *z*.

Refinement

$R[F^2 > 2\sigma(F^2)] = 0.052$	361 parameters
$wR(F^2) = 0.124$	H-atom parameters constrained
$S = 1.06$	$\Delta\rho_{\max} = 0.42 \text{ e } \text{Å}^{-3}$
4986 reflections	$\Delta\rho_{\min} = -0.37 \text{ e } \text{Å}^{-3}$

The merging *R* index is fairly high (0.124), indicative of rather modest crystal quality. This is also reflected in the final *R* indices and the overall precision of the molecular geometry. All H atoms were located in difference maps and then treated as riding atoms in geometrically idealized positions, with C—H = 0.95 (aromatic), 0.99 (CH₂) or 1.00 Å (aliphatic CH), and with $U_{\text{iso}}(\text{H}) = 1.2U_{\text{eq}}(\text{C})$.

Data collection: *COLLECT* (Nonius, 1999); cell refinement: *DIRAX/LSQ* (Duisenberg *et al.*, 2000); data reduction: *EVALCCD* (Duisenberg *et al.*, 2003); program(s) used to solve structure: *SIR2004* (Burla *et al.*, 2005); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *PLATON* (Spek, 2009); software used to prepare material for publication: *SHELXL97* and *PLATON*.

The authors thank the Centro de Instrumentación Científico-Técnica of the Universidad de Jaén and the staff for the data collection. JC thanks the Consejería de Innovación, Ciencia y Empresa (Junta de Andalucía, Spain), the Universidad de Jaén (project reference UJA_07_16_33) and the

Ministerio de Ciencia e Innovación (project reference SAF2008-04685-C02-02) for financial support. BI and AG thank Univalle, Colciencias and Universidad del Chocó for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SF3141). Services for accessing these data are described at the back of the journal.

References

- Aakeröy, C. B., Evans, T. A., Seddon, K. R. & Pálinkó, I. (1999). *New J. Chem.* pp. 145–152.
- Bernstein, J., Davis, R. E., Shimoni, L. & Chang, N.-L. (1995). *Angew. Chem. Int. Ed. Engl.* **34**, 1555–1573.
- Brammer, L., Bruton, E. A. & Sherwood, P. (2001). *Cryst. Growth Des.* **1**, 277–290.
- Burla, M. C., Caliandro, R., Camalli, M., Carrozzini, B., Cascarano, G. L., De Caro, L., Giacovazzo, C., Polidori, G. & Spagna, R. (2005). *J. Appl. Cryst.* **38**, 381–388.
- Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.
- Cunico, W., Capri, L. R., Gomes, C. R. B., Sizilio, R. H. & Wardell, S. M. S. V. (2006). *Synthesis*, pp. 3405–3408.
- Cunico, W., Capri, L. R., Gomes, C. R. B., Wardell, S. M. S. V., Low, J. N. & Glidewell, C. (2007). *Acta Cryst.* **C63**, o102–o107.
- Duisenberg, A. J. M., Hoof, R. W. W., Schreurs, A. M. M. & Kroon, J. (2000). *J. Appl. Cryst.* **33**, 893–898.
- Duisenberg, A. J. M., Kroon-Batenburg, L. M. J. & Schreurs, A. M. M. (2003). *J. Appl. Cryst.* **36**, 220–229.
- Howard, J. A. K., Hoy, V. J., O'Hagan, D. & Smith, G. T. (1996). *Tetrahedron*, **52**, 12613–12622.
- Insuasty, B., Gutiérrez, A., Quiroga, J., Abonía, R., Noguera, M., Cobo, J., Svetaz, L., Raimond, M. & Zucchini, S. (2010). *Arch. Pharm. Chem. Life Sci.* **343**, 48–53.
- Nonius (1999). *COLLECT*. Nonius BV, Delft, The Netherlands.
- Sheldrick, G. M. (2003). *SADABS*. Version 2.10. University of Göttingen, Germany.
- Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112–122.
- Spek, A. L. (2009). *Acta Cryst.* **D65**, 148–155.
- Thallapally, P. K. & Nangia, A. (2001). *CrystEngComm*, **27**, 1–6.